



# RSIAS

**ERSIAS**

**EDAS Revascularization for Symptomatic  
Intracranial Arterial Stenosis**

**PHASE II**

## **STUDY PROTOCOL**

### **EDAS REVASCULARIZATION FOR SYMPTOMATIC INTRACRANIAL ARTERIAL STENOSIS (ERSIAS) FUTILITY TRIAL**

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### Study design

The goal of the current study is to formally assess the safety and evaluate the likelihood that patients will or will not benefit from EDAS revascularization in cases of symptomatic intracranial arterial stenosis and absent or poor angiographic collaterals. To achieve this goal we designed a single-arm, prospective, futility trial of **EDAS Revascularization for Symptomatic Intracranial Arterial Stenosis (ERSIAS)**. The proposed trial will perform a futility evaluation of EDAS plus aggressive medical management against a predetermined threshold value based on the historical control group of aggressive medical management alone in the SAMMPRIS trial, applying the paradigm design of a futility phase II trial (Palesch et al., 2005).

ERSIAS PHASE II was conducted at UCLA and Cedars Sinai Medical Center with the support of the UCLA NeuroNEXT phase 2 network, the UCLA NETT clinical trial network, and the UCLA NIH SPOTRIAS Center Patient Access Core, which includes 39 Stroke Network partner hospitals, and in cooperation with the Departments of Neurosurgery, Stroke Neurology, Radiology and the Laboratory of Neuro-Imaging in both institutions. Our hypothesis is that EDAS combined with aggressive medical therapy is sufficiently promising to warrant definitive, pivotal trial testing. To test this hypothesis we will evaluate a primary endpoint of (1) stroke or death at 30 days after revascularization or (2) stroke in the vascular territory of the qualifying artery at one year, using a cut-off value derived from the historical control from the SAMMPRIS medical arm. Secondary clinical endpoints include: any disabling stroke or death for the duration of the study, myocardial infarction, non-stroke hemorrhage, and functional outcome at the end of follow-up. In the course of the trial, we also plan to evaluate the time course of collateralogenesis and perfusion improvement following EDAS revascularization. Our hypothesis is that EDAS will generate improved collateral circulation to territories at risk of stroke. To test this hypothesis we will evaluate a primary imaging endpoint of increase in at least one grade on the ASITN/SIR Angiographic Collateral Flow scale at one year.

### Patient selection

The futility threshold, or cut-off point below which the intervention will be considered futile has been calculated from the control group with impoverished collaterals in the SAMMPRIS and COSS medical arm. In order to reduce, as much as possible, variations from the reference population, we will use the exact inclusion and exclusion criteria employed in SAMMPRIS, with the additional requirement of demonstrated poor or non-existent collateral circulation on cerebral angiography. The rationale for enrolling in ERSIAS only patients with poor or no collateral circulation is based on (1) the evidence that from both WASID and SAMMPRIS that collateral poverty identifies patients at particularly high risk of stroke under intensive medical therapy (Liebeskind et al., 2011), and (2) the collateral enhancement goal of the EDAS procedure. Patients aged  $\geq 30$  years and  $\leq 80$  who have a recent history (within 1 month from enrollment time) of transient ischemic attacks (TIA) and/or non-disabling stroke who present to our institutions will be considered for inclusion. The SAMMPRIS inclusion and exclusion criteria have been described in detail by the SAMMPRIS investigators and we will strictly adhere to the same criteria (Chimowitz et al., 2011b). Table 1 describes the modifications for this study.

Study eligibility will be determined by any of the Vascular, Neurohospitalist, or Neurointensivist Neurology faculty who are not the PI or mentors of the study. It is part of the usual standard of care for patients with symptomatic intracranial stenosis

to undergo cerebral angiogram and MRI studies, including perfusion MRI. If the patient is considered a candidate for the surgical available standard of care

Inclusion Criteria	Exclusion criteria
1. All the SAMMPRIS inclusion criteria 2. Angiographic demonstration of inexistent or poor collaterals: American Society of Interventional and Therapeutic Neuroradiology (ASITN) / Society of Interventional Radiology (SIR) Collateral Flow Grades 0-2	1. Any of the SAMMPRIS exclusion criteria. 2. Intracranial tumor ( <b>including</b> meningioma) or any intracranial vascular malformation 3. History of cranial surgery on the side of the qualifying intracranial artery 4. Absence or severe atrophy of the superficial temporal on angiography 5. Presence of signs or symptoms of current infectious process

approaches for chronic cerebral hypoperfusion, including EDAS, the patients will be offered the surgical option of treatment. In addition to the usual consent for these procedures used in the clinical practice, patients will give written informed consent to participate in the study, including the additional follow-up visits and imaging studies.

Patients considered for inclusion who do not meet the exact inclusion/exclusion criteria of SAMMPRIS, but who have poor or no collaterals on angiography and no surgical contraindications are potentially surgical candidates. These patients will not be enrolled in the ERSIAS-1 study, but their information will be collected in a prospective registry. The rationale for this parallel data collection is that some of the inclusion and exclusion

criteria for SAMMPRIS were based on eligibility for angioplasty and stenting, such as the target stenosis of less than 14 mm in length, tandem stenosis, and etiology different than atherosclerosis, which are not expected to affect the potential effect and application of EDAS revascularization in those cases.

### *Treatment interventions*

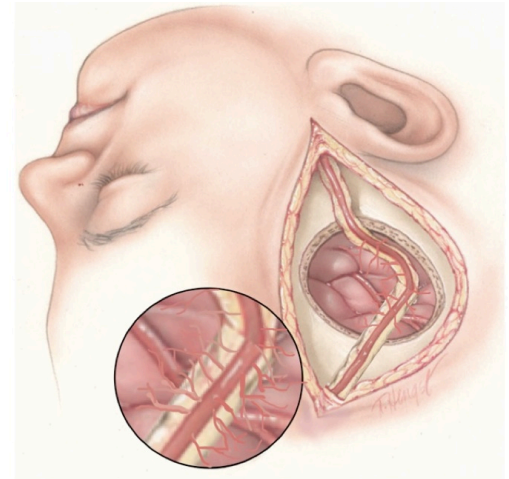
**Surgical management:** EDAS revascularization surgeries will be performed within 1 week of enrollment. The procedure technique has been described in detail in our prior publications (Dusick et al., 2011, Dusick et al., 2012). In summary, the operation is performed under general endotracheal anesthesia, with intraoperative electroencephalographic monitoring. Anesthesia will be directed to keep strict control of blood pressure to avoid hypotension with a goal systolic blood pressure above 120 mmHg. Higher limits may be set in patients who are typically hypertensive pre-operatively, generally aiming for a systolic blood pressure 20% above their baseline level, and not higher than 200 mmHg. Hyperventilation will be avoided to prevent vasoconstriction associated with hypocapnia. Patients receive prophylactic antibiotics within one hour of the skin incision, and they are suspended within 24 hours of the operation. Systemic hypothermia and/or barbiturates are not routinely used for neuroprotection as no temporary occlusion of intracranial arteries is done. The patients receive aspirin continuously, including the morning of the surgery. This requires conscientious surgical technique to achieve adequate hemostasis. Special attention is paid to construct the dural opening in a manner that preserves as many of the MMA branches as possible. Bipolar cautery of the dura will be kept to a minimum and the two layers of the dura are carefully peeled apart at the opening. The arachnoid of the subjacent brain will be opened widely using microsurgical technique. The adventitia of the STA is sutured to the edges of the dura prior to replacing the bone flap. The superior and inferior ends of the craniotomy are left with large openings to reduce kinking of the entry and exit points of the STA. The inner table of the bone flap is trimmed to reduce excessive compression of the artery. Typically the surgery includes the performance of additional burr holes in areas targeted by analysis of the angiogram and the perfusion studies (hypoperfused areas not adjacent to the main craniotomy). At these locations, the dura is opened carefully and the underlying arachnoid is opened under microscopic visualization.

**Surgeon selection:** Neurosurgeons will be certified to participate upon documentation of 5 consecutive previous EDAS or EC-IC bypass surgeries, with 80% or greater graft patency and less than 10% rates of stroke and death at 1 month. The surgeons will attend a training workshop with videotaped instructions of the standard EDAS technique for the study, as described above.

**Concomitant medical management:** Beginning immediately upon enrollment, all patients will undergo intensive medical treatment, executed following the SAMMPRIS model. All patients will receive intensive management of the primary risks factors (systolic blood pressure and low density lipoprotein [LDL]). They also will receive management of secondary risk factors (diabetes, non-high-density lipoprotein [non-HDL], smoking, weight, and exercise). As in SAMMPRIS, ERSIAS will provide the lifestyle modification program to enrolled patients for 2 years. The surgical strategy being tested in ERSIAS does require one time-limited modification of the SAMMPRIS antithrombotic regimen: During the 1-7 days between enrollment and surgery and during the first 15 postoperative days, patients will receive aspirin 325 mg daily but not clopidogrel, due of the increased surgical bleeding risk associated with clopidogrel. Once the risk of surgical bleeding has resolved, clopidogrel will be added, as per the SAMMPRIS medical therapy protocol.

### *Patient Follow-up*

All patients will be followed for the duration of the study. Patients will be examined at enrollment by the neurosurgeon performing the operation and a neurologist with stroke expertise independently. Following treatment, formal study visits will be performed with the first visit 4 days after surgery. Patients will be evaluated again 1 week and 2 weeks following surgery. Subsequently, follow-up visits will occur at 30 days, 6 months, and then every 6 months until the first of the following: 90 days after a primary endpoint, death, or the close-out visit for the trial. At each visit, medications will be reviewed, blood pressure is recorded and the patients will be examined to determine if any adverse effects have occurred and to record the neurological assessment scales.



EDAS revascularization. The donor artery is placed in closed proximity to the superficial brain arteries. A network of collaterals forms between the donor artery and the adjacent brain vessels without a surgical anastomosis

Clinical outcome assessments will be performed by members of the Stroke Centers Vascular neurologists who are not part of the surgical team. Patients lost to follow up will be censored at last contact date

### *Angiography imaging*

Diagnostic angiograms before surgery are obtained as part of patient standard care and will be used to define the degree of stenosis of the qualifying vessel, potential exclusion criteria (i.e. tandem stenosis) and the degree of collateral flow. The ASITN/SIR Collateral Flow Grading System will be used to determine the extent of collateral flow to the ischemic territory. Angiograms, as per usual postoperative care, are repeated at 6 months and 12 months after EDAS revascularization.

### *Clinical endpoints*

The primary study endpoint is the composite of (1) any stroke or death within 30 days after enrollment, or (2) any ischemic stroke or death attributable to ischemia in the territory of the qualifying artery at one year. All patients will be followed for up to 2 years after enrollment, with data through the end of year 1 contributing to the primary analysis and data through the end of year 2 contributing to secondary analyses. As in SAMMPRIS, ischemic stroke is defined as a new focal neurological deficit of sudden onset, lasting at least 24 hours and not associated with CT or MRI findings of hemorrhage. Symptomatic cerebral hemorrhage is defined as parenchymal, subarachnoid or intraventricular bleeding detected in any imaging modality that is associated with new neurological deficits. Hemorrhage would only contribute to the primary endpoint if it occurs within 30 days after surgery.

Secondary endpoints include: (1) disabling stroke; (2) any stroke or death after 30 days; (3) myocardial infarction; (4) major non-stroke hemorrhage (systemic hemorrhage, subdural or epidural hemorrhages); (5) functional outcome at the end of follow-up measured by the modified Rankin scale and Barthel Index; and (6) cognitive outcome at the end of follow-up measured by the Montreal Cognitive Assessment. All potential endpoints are adjudicated by an independent stroke neurologist, not part of the surgical team. Suspected strokes will be confirmed by MRI or CT imaging. NIHSS will be recorded.

All serious adverse events occurring during the study participation will be recorded. A serious adverse event is defined as one that is fatal, life-threatening, permanently or substantially disabling, requires or prolongs hospitalization, or requires medical or surgical intervention to prevent one of the above outcomes whether or not considered to be related to the intervention. Each SAE will be reported to the Study Monitoring Committee within 7 working days. A summary report of all serious adverse events will be generated for review at every meeting with the Study Monitoring Committee (SMC).

### *Imaging endpoints*

The primary imaging endpoint is increase by at least one grade on the ASITN/SIR Angiographic Collateral Flow scale at one year.

### *Sample size and statistical considerations*

Following the statistical framework for a futility study described by Palesch et al (Palesch et al., 2005), we will compare the endpoint of the proposed trial against a predetermined threshold value reflective of an estimated clinically meaningful impact, calculated based on the results of the medical arm of SAMMPRIS.

Proportion of unfavorable outcomes in the historical control: The probability of occurrence of the primary endpoint of stroke or death within 30 days of enrollment or ischemic stroke in the territory of the qualifying artery beyond 30 days after enrollment in the overall SAMMPRIS medical arm was 12.2% at one year. In ERSIAS, we will enroll the subset of such patients with demonstrated poor or no collateral circulation. This fact is expected to increase the rate of failure, based on the observations of Liebeskind et al in the WASID dataset at 1 year and the SAMMPRIS dataset at 1 month (Liebeskind et al., 2012). In the WASID population, among individuals with severe stenosis ( $\geq 70\%$ ), the event rate was increased 6-fold in patients with poor or no collateral circulation. This observation can be applied to SAMMPRIS one-year data to derive the control group rate. Among 186 patients in the medical arm of SAMMPRIS with angiographic information available for evaluation of collaterals, 120 had poor collaterals, indicating that 64.5% of the SAMMPRIS population falls in the high-risk stratum to be enrolled in ERSIAS. Assuming the same 6-fold risk among poor/no collateral patients versus good collateral patients in SAMMPRIS as in WASID, the event rate at 1 year among poor/no collateral patients is expected to be 17.3%.

Threshold value of clinically meaningful impact: Based on our preliminary experience we anticipate a 30% relative reduction (5% absolute reduction) in the primary endpoint at one year for EDAS plus aggressive medical management, which represents a highly clinically meaningful effect size for EDAS treatment.

Sample size: We derived the sample size required to power the trial to test the difference between two binomial event rates using the method of Farrington and Manning (Farrington and Manning, 1990) as implemented in R package gsDesign (Anderson, 2011). An estimated sample size of 52 patients will be necessary to detect a  $\Delta$  of 0.05, with a one-sided alpha of 0.10 and a beta of 0.10 - acceptable parameters for a non-definitive, futility study (Palesch et al., 2005, Levin, 2005). It is important to emphasize that in a futility trial, as the goal is not demonstration of effectiveness, alpha is to be interpreted as the chance of calling an effective treatment ineffective, and beta the chance to fail to identify an ineffective treatment. Given the severity of the clinical problem (IAS), we do not want to miss an effective intervention in a middle development stage. If futility is not demonstrated we may proceed to a phase III trial of efficacy, with smaller error probabilities (values of beta and alpha).

Data analysis: The proportion of patients undergoing EDAS revascularization that reach the primary endpoint ( $p_{tx}$ ) will be compared with the failure rate from SAMMPRIS medical arm ( $p^*$ ). The hypothesis tested in this proposal can be expressed as  $H_0: p_{tx} \leq p^* - \Delta$  versus  $H_A: p_{tx} > p^* - \Delta$ . Failure to reject the null hypothesis with an alpha set at 0.10 and beta at 0.10 will warrant further testing in a phase III trial. We will also perform logistic regression analysis to include any variables that could be significantly different between ERSIAS-1 subjects and the comparison group from the SAMMPRIS medical arm. However, every effort will be made to avoid deviations from SAMMPRIS in the ERSIAS-1 trial. The logistic regression analysis will also be carried out for the registry patients and the analysis of the secondary endpoint of MRI perfusion data. With the exception of the primary analysis for futility of the proportion of the primary endpoint, interpretation of any other  $P$  values will be made with caution because of the exploratory nature of this study. For the analysis of the imaging primary endpoint of improvement of at least 1 grade in the ASITN/SIR Collateral Flow Grades, in a population of 55, an effect of 80% improvement in collateral flow would have a 95% confidence interval of 67.9% - 89.0% as determined by the mid-P method.

Propensity Score Matching Control Group: In order to correct for the effects of including patients with intracranial vascular occlusion and the high-risk characteristics of our expected population compared to the SAMMPRIS trial, we will conduct a propensity score matching (PSM) to the patients in the medical arms of the SAMMPRIS trial and to patients in the medical arm of COSS that had demonstrated angiographic intracranial atherosclerosis and occlusion. The COSS data collection forms allow for identification of patients which carotid occlusion was associated to intracranial atherosclerosis. This subset of COSS patients will be used for the PSM. PSM will be performed for conditioning on the selected confounding covariates: stenosis vs. occlusion, age, gender, history of diabetes, hypertension, hyperlipidemia, previous stroke, and coronary artery disease.

If some risk factors cannot be closely matched, they will be balanced to have in the control group a lower proportion of the risk factors that can increase the risk for recurrent stroke and death. The expected effect of these imbalanced factors would be in favor of the PSM control group.

### *Study Monitoring*

We will appoint, in consultation with the NINDS, a Study Monitoring Committee with one statistician and three physicians (one vascular neurologist, one neurosurgeon, and one neurocritical care specialist) who have not participated in the design of this study and will not be part of the project, unless the NINDS requires otherwise. The SMC will monitor the study for patient safety, review all serious adverse events, meet periodically with the investigators, and their activities will be coordinated with the NINDS PD, who would be asked to approve all monitoring procedures and could participate in the SMC meetings. Final determination of a formal stopping rule will be the prerogative of the appointed SMC. We have included in the statistical approach one interim analysis when 50% of the patients have their day 30 evaluation completed.

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